REMARKS

Claims 1-69 were originally presented in the present application. Claims 1-16, 18-30 and 56-67 are currently pending. Claims 2, 4, 13, 14, and 56-67 are cancelled herein by amendment and without prejudice to Applicants' rights to pursue these claims in other patent applications.

Amendments to the Claims

Applicant has currently amended Claims 1, 3-12 and 15. Claims 70 is new. As noted above, Claims 2, 4, 13, 14, and 56-67 are cancelled herein by amendment and without prejudice to Applicants' rights to pursue these claims in other patent applications.

Support for Claim Amendments

Support for each claim amendment can at least be found in the specification as originally filed as follows.

For "A process for extending lifespan of a mammal or a mammalian cell beyond a generic expected lifespan for said mammal or mammalian cell" in Claim 1, see page 16, lines 11-14 ("The lifespan increased by the instant invention is the expected average length of time (from birth to death) that a metazoan would be expected to live (i.e., "generic" expected lifespan), if that metazoan were not utilizing the process of the instant invention").

For "a therapeutically effective amount", see page 12, line 16-17 ("by administering a therapeutically effective amounts of antioxidants that result in an extended metazoan or metazoan's cell, lifespan.")

For "pharmaceutically acceptable salts of any of the foregoing, pharmaceutically acceptable esters of any of the foregoing, and pharmaceutically acceptable amides of any of the foregoing" in Claim 1, see page 13, line 1-3 ("C_{60} compounds of the instant invention, which are

referred to as carboxyfullerenes, have been mono- or multiply-derivativized with malonic acid, or the pharmaceutically acceptable malonic acid salts, esters and amides").

For "wherein said mammal or mammalian cell is not selected for a disability" in Claim 1, see page 21, line 4-5 ("Mice shipped from this colony were not selected in any way for health, tumors or other disabilities").

For "thereby extending the lifespan of said mammal or said mammalian cell beyond the generic expected lifespan for said mammal or said mammalian cell by up to about 32%. " in Claim 1, see page 10, lines 10-13 of the specification ("This calculation includes one C_3-treated mouse which is still alive as of February 21, 2002, and whose lifespan was included as of this date. Continued survival by this mouse will further increase the average difference in lifespan, and will decrease the *p* value (increase the significance"). Also see Figure 4 data point for C_3-treated mouse that was alive at 33 months.

For "The process as set forth in Claim 1 wherein an expected lifespan of the mammal or mammalian cell prior to treatment is the generic expected lifespan for said mammal or mammalian cell."(new Claim 70), see page 16, lines 11-15 ("The lifespan increased by the instant invention is the expected average length of time (from birth to death) that a metazoan would be expected to live (i.e., "generic" expected lifespan), if that metazoan were not utilizing the process of the instant invention. The lifespan of the control mouse used in this example represents the generic "expected lifespan".")

Claim Rejections under 35 U.S.C. §112, first paragraph

Examiner rejected previously pending Claims 1-16, 18-30 and 56-67 under 35 U.S.C. §112, first paragraph, alleging that the specification, while being enabling for extending the lifespan of mice, does not reasonably provide enablement for extending the lifespan of metazoans or metazoan cells. With respect to enablement of compounds other than C_3 tris malonic acid C60, the Examiner did acknowledge that the evidence introduced in the Declaration of Dr. Laura Dugan does provide enablement of the compounds "C3", "Penta", "C3-lite" and compound $C_{60}(C(COOH)_2)_n$, where n=1,2, or 3 (Page 10, 2nd paragraph of 9/19/2005 Office Action). However, the Examiner maintained that neither the specification nor the Declaration provide enablement for the "Tetra" compound or all of the claimed C(sub)60 compounds represented in the formula of the then pending Claim 1.

Enablement of increased longevity in organisms besides mice

The claims as currently amended are drawn to a method of extending the lifespan of a mammal or a mammalian cell and thus render the Examiner's arguments as to enablement of metazoans moot. However, the Examiner has alleged that the specification has only enabled methods of increasing the lifespan of mice.

In reviewing relevant case law related to enablement of claims to therapeutic uses, the Applicant finds little support for the proposition that such claims are only enabled for the particular model system in which they were tested. To the contrary, analysis of the available case law indicates that the enablement requirement of 35U.S.C.§112 for claims directed to asserted therapeutic uses is even satisfied in cases where the compounds were only tested in vitro or

model in vivo systems (i.e., mice). For example, in *Cross v. Iizuka* (753 F.2d, 1040), the Board of Appeals held that a Japanese priority application where the compounds in question had only been tested in an in vitro microsome system met the how-to-use requirement of 35U.S.C.§112 even in the absence of disclosed dosages. With respect to in vivo models, disclosure of anti-tumor activity of compounds in mice and in cultured cells was also deemed sufficient to reverse a 35U.S.C.§112 rejection of claims to directed the antitumor compounds (*In re Brana*, 51 F.3d 1560). A particularly relevant portion of *In re Brana* reads:

> "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. § 112 ¶ 1."

Taken together, these cases clearly hold that actual testing outside of a relevant in vitro or in vivo model system is not required to meet the enablement requirements of 35 U.S.C. § 112 with respect to therapeutic uses. To limit the instant invention to treatment of mice based on the enablement requirements of 35 U.S.C. § 112 would thus be inconsistent with existing case law. Limiting the instant invention to treatment of mice as suggested by the Examiners would also set

forth a standard of enablement for therapeutic methods that could only be met if the invention first passed through Phase II clinical trials involving human subjects. Applicants point out that only a small fraction of previously patented inventions directed to therapeutic treatments would have met such a standard for enablement.

With respect to enablement of this instant invention in mammals and mammalian cells, the mouse model system disclosed in the specification is as a well documented system for identifying treatments that result in longevity increases. In this regard, Applicant again cites the selection of mice by The National Institute of Aging as a model system for the "Interventions Testing Program" to obtain results on anti-aging drugs or treatments. Although the reference provided may not explicitly state that mice will provide information that can be translated to humans, it is self-evident that the government would not support a program of this magnitude if there was not a reasonable expectation that the results obtained in mice could be extrapolated to other mammals and humans in particular. Mice have also been used by the National Institute of Aging to identify biomarkers of aging for use in mammals such as humans (see Turturro et al, 1999). The Applicant has also presented scientific evidence that reductions in oxidative stress can result in lifespan increases even in non-mammalian organisms such as the roundworm *C.elegans* (Melov et al., 2000) and the fruit fly *Drosophila* (Sohal and Weindruch, 1996). One skilled in the art would thus have ample basis for believing that the instant invention, which discloses administration of an effective catalytic antioxidant that results in increased lifespan in mice, has enabled treatments for the increasing the lifespan of other mammals. Finally, we again note that enablement requires only necessary that "the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." *Amgen Inc. v.*

Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1334 (Fed. Cir. 2003), *citing Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365 (Fed.Cir.1997); *In re Vaeck,* 947 F.2d 488, 495, (Fed.Cir.1991). The instant application clearly describes how to make and administer the compounds of the invention to mammals such as mice and humans. and additionally provides evidence of how to administer the compounds of the invention to a standard model mammal (i.e., mice). Synthesis of carboxyfullerene compounds is described in Example 1. Administration methods, formulations and dosages on Page 13, line 20 through Page 16, line 9 of the specification.

Enablement of C(sub)60 derivatives other than C(sub)3 tris malonic acid C(sub)60

In the Office action of September 19 2005, the Examiner indicated that the evidence contained in the Affidavit submitted by Dr. Laura Dugan supported the enablement of the compounds "C(sub)3", "Penta", and "C(sub)3-lite" under 35U.S.C.§112. The Examiner also indicated that the disclosure of Choi et al. (U.S. Patent No. 6,265,433) supported the enablement under 35U.S.C.§112 of compounds $C_{60}(C(COOH)_2)_n$, where n=1,2, or 3. The claims as currently amended specify *e,e,e* $C_{60}(C(COOH)_2)_2(C(CHCOOH)$, *e,e,e* $C_{60}(C(CHCOOH))_3$ and $C_{60}(C(COOH)_2)_n$, where n=1,2, or 3. As indicated in item 5 on the second page of Dr. Dugan's affidavit, *e,e,e* $C_{60}(C(COOH)_2)_2(C(CHCOOH)$, corresponds to "Penta" and *e,e,e* $C_{60}(C(CHCOOH))_3$ corresponds to "C(sub)3-lite". The claims as amended are thus drawn to the compounds identified by the Examiner as enabled (Page 10, Paragraph 2 of the September 19, 2005 Office Action).

The Examiner made the statement on page 11 of the September 19, 2005 Office Action "that because "Tetra" lacks reduced NMDA receptor toxicity, it would not logically follow that such a compound would have the same activity as "C_3", since it lacks one of the major properties of "C_3", absent any factual evidence to the contrary". For the purpose of clarifying the prosecution history, the Applicant notes that the exhibits accompanying Dr. Dugan's affidavit do not appear to show that Tetra "lacks reduced NMDA receptor toxicity" as asserted by the Examiner.

Claim Rejections under 35 U.S.C. §103

I. *Joint Inventors*

Applicant acknowledges their obligation under 37 CFR§1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §102(e), (f), or (g) prior art under 35 U.S.C. §103(a). To Applicants' best knowledge, all subject matter of the claims of the instant invention was commonly owned at the time of invention of each of the claims.

II. *Unpatentable over Lei et al. and Stedman's Medical Dictionary in view of Chiang, Choi et al. and WO 97/46227.*

Examiner has maintained the rejection then pending Claims 1-32 and 56-69 under 35 U.S.C. §103(a) as being unpatentable over Lei et al. (U.S. Patent No. 6,777,445, cited by Examiner) and Stedman's Medical Dictionary (cited by Examiner) in view of Chiang (U.S. Patent No. 5,648,523, cited by Examiner), Choi et al. (U.S. Patent No. 6,265,443, cited by

Applicants) and WO 97/46227 ("WO '227", PCT counterpart of Choi et al. '443, cited by Applicants). Lei et al. pertains to the use of C_{60} derivatives for increasing the survival of mice challenged with infectious bacteria or viruses. In maintaining this rejection, the Examiner has alleged that the definition of lifespan contained in the specification of the instant application, which reads as "the average expected length of life of a kind of organism or cell in a particular environment" does not distinguish this invention as the infected mouse of Lei et al. is considered by the Examiner "to be an organism in the particular environment of infection". Consequently, the Examiner has maintained the position that the instant invention is obvious over the primary reference of Lei et al. and Stedman's Medical Dictionary in view of Chiang, Choi et al. and WO 97/46227.

The Applicants maintain that there is no motivation or suggestion to combine the cited references to extend lifespan, that the references themselves provide no reasonable expectation that the compounds would have extended lifespan, and that the references do not teach or suggest the key claim limitation of extending the lifespan of a mammal or a mammalian cells in view of the definition of lifespan provided by both the specification as a whole and the explicit definition of the term therein. What is at issue is if one of skill in the art would construe the term "extending lifespan" as used in the instant invention and claims to include increasing survival by defeating bacterial and viral infections.

With respect to the explicit definition of lifespan provided by the specification (i.e., "the average length of life of a kind of organism in a particular environment"), one skilled in the art would construe the term "environment" to encompass "infection" (i.e., an "organism in the particular environment of infection"). To the contrary, we believe that one skilled in the art

would understand the term environment as it is more commonly defined (i.e., "The totality of circumstances surrounding an organism or group of organisms, especially the combination of external physical conditions that affect and influence the growth, development, and survival of organisms." *The American Heritage® Stedman's Medical Dictionary Copyright © 2002, 2001, 1995 by Houghton Mifflin Company. Published by Houghton Mifflin Company.)* Note that the definition of the term environment refers to what *surrounds* or is *external* to the organism. In contrast, "infection" is defined by *The American Heritage® Stedman's Medical Dictionary* as "1) Invasion by and multiplication of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms. 2) An instance of being infected. 3) An agent or a contaminated substance responsible for one's becoming infected. 4) The pathological state resulting from having been infected. 5) An infectious disease." (*The American Heritage® Stedman's Medical Dictionary. Copyright © 2002, 2001, 1995 by Houghton Mifflin Company.)* Note that infection is regarded as an intrinsic condition or state that occurs when a microorganisms invades a host (i.e., is internalized).

With respect to the understanding of the term "lifespan" provided by the specification as a whole, one of skill in the art would not construe the term "lifespan" to include the state of infection. First, one skilled in the art would look to the discussion and references cited in the background section of the application to determine if this invention concerns increasing the lifespan of organisms infected with bacteria or viruses. Discussion of increasing lifespan by combating any type of infection is conspicuously absent from any section of the specification or references cited therein. In fact, at least two of the cited references explicitly point to the use of

"specific pathogen-free" animals and conditions for the purpose of determining life span increasing effects (see Kitani et al., Life Sciences 52:281-288; page 282; also see Carrillo et al. Life Sciences 67: 2539-2548, page 2541). Clearly, these cited studies to investigate life span increasing treatments took explicit steps to avoid the occurrence of infection that would potentially confound the results. Similarly, the specification states that the mice in this particular life span study "were not selected in any way for health, tumors, or other disabilities" (see Example 2 of the specification). The specification also states that the mice were obtained from the National Institute of Aging Rodent Colony that are understood by those skilled in the art to be maintained under specific pathogen free conditions. Consequently, one skilled in the art would understand that the mice used in these studies are also specific pathogen free and that these studies were not performed "in the environment of an infection". Furthermore, the claims as currently amended specify that the "mammal or mammalian cell is not selected for a disability" and thus clearly distinguish the claimed method of the instant invention from Lei et al. where the animals were selected for the disability of a bacterial or viral infection.

Applicant therefore submits that the references do not teach or suggest the key claim limitation of increasing lifespan. For these reasons and those cited above, the Applicant submits that the rejection of the currently pending claims under over Lei et al. and Stedman's Medical Dictionary in view of Chiang, Choi et al. and WO 97/46227. 35U.S.C.§103 is improper and request that it be withdrawn.

Non-Statutory Provisional Double Patenting Rejection

Previously presented and currently pending Claims 1, 4-32 and 56-69 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 22-33 of co-pending U.S. Patent Application No. 10/373,425. This double patenting rejection is at this point moot as the Applicants have cancelled Claims 22-23 of co-pending U.S. Patent Application No. 10/373,425 in the Election and Reply to Restriction filed August 12, 2005 with the U.S. Patent and Trademark Office.

Issues raised in December 5, 2005 Interview Summary

In the Interview Summary, Examiners indicated that the claims should "reflect the increase in lifespan actually demonstrated by the use of such compounds." Examiners have also provided applicants with two references (Hayflick,L. Mech. Aging and Develop. 14:59-79,1980; and Hayflick, L. Sci. Am.: 242(1):58-65). The Hayflick references are apparently concerned with the issue of obtaining immortality of organisms and cultured cells. Applicants have amended Claim 1 to reflect the increases in lifespan obtained by practice of the invention (i.e., " thereby extending the lifespan of said mammal or said mammalian cell beyond the expected generic expected lifespan for said mammal or said mammalian cell by up to about 32%"). Support for this amendment can at least be found on page 10, lines 10-13 and in Figure 4 as noted in the previous "Support for Claim Amendments" section. Although an average lifespan increase of 20% corresponding to a lifespan 29 months was demonstrated by the applicants in the treated mice, inspection of Figure 4 reveals that four (4) of the nine (9) treated mice lived beyond 29 months and thus had lifespan increases of greater than 20%. One treated mouse was still alive at

33 months. A simple calculation reveals that a lifespan of 33 months corresponds to a 32% increase in lifespan relative to the average lifespan of 23.5 months exhibited by the untreated control mice (i.e., (33-23.5)/23.5=0.32). Since the mouse was still alive at 33 months, use of the term "about" in the claim is appropriate. Applicants respectfully submit that the claim phrase "about 32%" meets the requirements of 35 U.S.C. §112, second paragraph because a skilled practitioner in the pharmaceutical arts to which this Application is directed would understand the meaning of the term "about" with respect to the degree of lifespan increase obtainable with the instant invention in light of the disclosure of the specification. This position is in accord with recent rulings of the Federal Circuit Court indicating that:

> "broadening usages as 'about' must be given reasonable scope; they must be viewed by the decision maker as they would be understood by persons experienced in the field of the invention... Although it is rarely feasible to attach a precise limit to 'about,' the usage can usually be understood in light of the technology embodied in the invention. When the claims are applied to an accused device, it is a question of technologic fact whether the accused device meets a reasonable meaning of 'about' in the particular circumstances." *Modine Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1554 (Fed. Cir. 1996); *see also, Merck & Co. v. Teva Pharmaceuticals USA Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) (holding "the term 'about' should be given its ordinary and accepted meaning of 'approximately' unless patentee clearly redefines 'about' in the specification.").

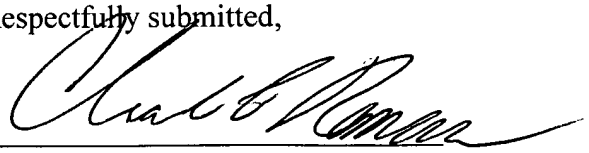
Finally, the Examiners also indicated in the Interview Summary that "there may be further issues with regard to enablement in light of ... information regarding efficacy of biological nanparticulate (sic) compositions". For the purposes of clarifying the prosecution history, Applicants simply note for the record that no information regarding efficacy of biological nanparticulate or nanoparticulate compositions has been provided or brought to their attention by the Examiners.

CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant respectfully requests that the Examiner reconsider and withdraw each rejection. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that a personal communication will expedite prosecution of this application, she is invited to telephone the undersigned agent at the number provided.

Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,



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